Effect of Calcium Channel Blockers on Arterial Stiffness and Function

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Calcium channel blockers were discovered at 1963, and verapamil were appeared as first drugs. After addition of nifedipine, diltiazem and other new drugs, calcium channel blockers are most commonly used drug as a cardiovascular drug. Calcium channel blockers are used in the management of cardiovascular disease, hypertension and angina pectoris. With a better understanding of calcium handling of cells, calcium channel blockers have improved therapeutic benefits and minimized untoward effects.

**Action mechanism of calcium channel blockers**
Calcium ions are vital in many biologic processes. They involved in a variety of enzymatic reactions, activation of excitable cells, and coupling of electrical activation. Calcium channel blockers are drugs that block calcium influx through calcium channels in excitable membranes. When calcium channel blockers are given, they exert main effect on vascular smooth muscle and myocardial cell. This tissue specific action is important and depends on heterogenicity of calcium channels.

**Type of calcium channels**
There are three types of calcium channels, voltage sensitive, receptor operated (cardiac muscle and vascular smooth muscle) and stretch operated channels (some blood vessel). Until now, voltage sensitive channels are now major targets for many calcium channel blockers. Tsien et al\(^1\) identified 3 types of voltages gated calcium channel. They included L-type (long lasting, large channels), T-type (transient, tiny channels), and N-type (neuronal, neither L nor T) channels. They are classified according to their activation and inactivation kinetics, conductance, ion specificity and sensitivity to drug and toxin.

**L-type channels**
These type channels are distributed in many tissues particularly in heart, smooth, and skeletal muscles. These type channels play a significant role in the excitation-contraction coupling of the cardiovascular system. They require a significant level of
depolarization for activation and are termed as high threshold channels. Most of calcium channel blockers, including verapamil, nifedipine, diltiazem, nitrendipines, nimodipine, nisoldipine, isradipine, amlodpine, felodipie, lacidipine and lercardipine are act on L-type channel.

**N-type channels**
These type channels are widely distributed in neurons. Like L-type channel, these type channels require a significant level of depolarization for activation. Cilnidipine blocks both L and N-type channels.

**T-type channel**
These type channels start to open with weak depolarizations reaching voltages much negative than those required to activate other voltage gated calcium channels and currents are transient. Recently T-type calcium channels are demonstrated as important channels for the regulation of arterial tone and cell growth. Thus, T-type calcium channels may be a potential target for vasoactive agents, and recently T-type calcium channel blocker (mibefradil) is developed. Although mibefradil was withdrawn rapidly because of drug interaction contraindications, it had a favorable hemodynamic and therapeutic profiles with negative chronotropy without negative inotropy, with effective vasodilation of coronary arteries, and without reflex sympathetic activation. However, mibefradil is not T-selective and it has a significant action through L-type channel and other type of calcium channels. In addition to midbefril, the newer dihydropyridines, manidipine, nilvadipine, and efonidipine are considered to block both L and T-type channels. P/Q type channels were also proposed.

**Arterial stiffness and calcium channel blockers**
Increased arterial stiffness is a hallmark of the aging process and the consequence of various diseases, and has been recognized as a strong independent predictor of cardiovascular event, such as myocardial infarction, heart failure and stroke, in several cardiovascular disease and chronic renal failure. Stiffening of large arteries increases the amplitude of the pressure wave and enhances the propagation velocity of the pressure wave. This leads to earlier return of reflected pressure waves to the central aorta, where they augment central pulse pressure. This increased load of central pulse pressure may promote ventricular and vascular hypertrophy and fibrosis. The elastic property of artery is exerted by media, containing elastin fibers, collagen fibers and smooth muscle. Changes of elastic
property of arterial wall, especially media leads to increase in arterial stiffness. Aging process induces increase in arterial stiffness. With increasing age, progression of atherosclerosis, degenerative changes in arteries cause arterial dilatation and thickening of arterial wall, and this change leads to increase in arterial stiffness. High arterial distending pressure increases arterial stiffness. Chronic rise in blood pressure cause recruitment and accumulation of less extendible collagenous fibers in arterial media, and makes arteries stiffer. In addition to high blood pressure, endothelial dysfunction causes increased arterial stiffness. Diabetes, chronic renal failure and other disorders causing rapid progression of atherosclerosis increase arterial stiffness.

Antihypertensive drugs have two major effects: reduction of blood pressure and direct effect on the vessel wall. Reduction of blood pressure and arterial stiffness may be associated with a reduction in cardiovascular risk. Possibly, reduction of arterial stiffness by antihypertensive agents depend not only reduction of blood pressure but also modification of structural component of vascular wall. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are well known anti-hypertensive agents to reduce arterial stiffness. And some calcium channel blockers reported to reduce arterial stiffness.

Data for the effects of calcium channel blocker on arterial stiffness are limited. Calcium channel blockers have been shown favorable short-term effects on large arterial stiffness in some studies, but not in other studies. Acute administration of calcium channel blocker improved arterial hemodynamics including reduction of pulse wave velocity. Although long-term above 6 months administration of calcium channel blockers improved arterial stiffness, several trials of 2 or 3 months administration of calcium channel blocker failed to improve arterial stiffness. Munakata et al compared nifedipine with valsartan on the effects of systemic arterial stiffness. In this study, 3 months administration of nifedipine showed no significant reduction in brachial-ankle PWV (baPWV). Takami et al also reported decrease in baPWV 3 months after administration of valsartan, temocapril or cilnidipine, but not after nifedipine CR. However 8 weeks administration of nifedipine decreased aortic PWV measured by ultrasound. Until now, there is no negative result on the improvement of arterial stiffness after long-term administration of calcium channel blockers. Amlodipine, nitrendipine, nicardipine and felodipine improved after long-term treatment.

The variable result for short-term effect may be from different measurement methods and different target calcium channels. Takami et al and Munakata et al measured PWV from brachial artery to ankle artery. baPWV has 3 different PWV, heart-brachial PWV, heart-femoral PWV and femoral-ankle PWV. Brachial artery and aorta are elastic
conduit artery. Femoral artery is muscular artery. Nifedipine is L-type calcium channel blocker, but cilnidipine is L- and N-type calcium channel blocker, and cilnidipine has antiproliferative effects of vascular smooth muscle cells.27 Although short-term administration of amlodipine failed to improve arterial stiffness,21 6 months administration decreased aortic PWV.24 Furthermore, recent study demonstrated reduction of carotid intima-media thickness after 2 years treatment of amlodipine.28 These results indicate that long-term effects of calcium channel blocker on arterial stiffness may not solely be from lowering of blood pressure.

In conclusion long-term calcium channel blockers may have favorable effects on arterial stiffness, and these effects may from lowering of blood pressure and antiproliferative action. Antiproliferative action of calcium channel blocker may be exerted by different calcium channels, N- and T-type. We need further investigation to clarify the effects of calcium channel blockers on arterial stiffness and the involved mechanisms.

References
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